REMARKS

Claims 1, 3-7, 9, 10, 21-28, 30-33, 35 and 36 presently appear in this case. No claims have been allowed. The official action of October 30, 2003, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a fused chimeric protein that is a linear genetically-engineered molecule of amino acid residues connected by peptide bonds. The chimeric protein is produced by fusing at the level of cDNA, DNA encoding at least one cell-targeting moiety, and DNA encoding at least one cell-killing moiety. The cell-targeting moiety is Met-GnRH or a Met-GnRH analog that specifically binds to GnRH binding sites on Caco2 adenocarcinoma cells. The cell-killing moiety is preferably a bacterial toxin, such as *Pseudomonas* exotoxin (PE). The invention further relates to pharmaceutical compositions and methods of treating various conditions by administering the chimeric protein of the present invention. Among the conditions that may be treated are adenocarcinomas and hepatocarcinomas, benign uterine leiomyoma, extrauterine endometriomas, benign hyperplasia of prostate or breast, and pituitary tumor adenoma.

Claims 1-7, 21 and 23-35 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Nett in view of Chaudhary (1989) and Chaudhary (1987), and as evidenced by the present specification. The examiner states that Nett teaches conjugation of GnRH to toxins such that GnRH is used to target

cells bearing GnRH binding sites and the toxin is employed to kill the cells. The examiner states that Nett teaches production of the toxins by recombinant DNA technology and that the toxin can be PE. The examiner states that the GnRH/toxin conjugates can be used for treatment of the prostate and breast and endometriosis. The examiner concedes that Nett does not teach a plasmid or methods for ligating the oligonucleotide encoding GnRH to an oligonucleotide encoding a toxin to produce a chimeric toxin molecule. The examiner states that these deficiencies are made up by the teachings of Chaudhary 1989 and 1987, which teach a method of producing a fusion protein toxin comprising an immunoglobulin and a mutated form of PE and methods of treating cancer. The examiner considers it to have been *prima facie* obvious to produce a fusion protein comprising the ten amino acids of GnRH wherein the oligonucleotide encoding the GnRH is ligated upstream to DNA encoding a mutated form of PE. The examiner states that the product obtained by the combination of Nett and Chaudhary would result in the claimed molecule and have all of the properties recited, and would obviously target adenocarcinoma cell-binding sites. This rejection is respectfully traversed.

The chimeric protein of the present invention has a structure that is different from that of the conjugate of Nett, and this structural difference allows it to target and kill adenocarcinoma and hepatocarcinoma cells, including non-hormone dependent adenocarcinoma cells. Prior to the present

invention it was not known that these cells had GnRH binding sites. The difference in structure permits a difference in binding specificities between the two structures, which difference would not have been obvious to one of ordinary skill in the art reading Nett and the two Chaudhary references. While the examiner is correct that, if it were obvious to combine Nett and the two Chaudhary references, one would obtain a chimeric protein that falls within the scope of the present claims, the examiner is incorrect in ignoring the unexpected results obtained by the present invention which would not have been apparent to anyone reading Nett and the two Chaudhary references.

The fusion protein of the present invention is produced bacterially and, thus, will always be preceded by a Met residue, as is shown in Figure 1C of the present specification. This is one of the features that differentiate the targeting moiety of the chimeric protein of the present invention and that of Nett. In order that this differentiation will be more clear, the present specification has been amended to always refer to the targeting moiety on the chimeric protein of the present invention as Met-GnRH, i.e., GnRH preceded by a Met residue.

As Figure 1 of the previously-submitted Declaration of Dr. Haya Lorberboum-Galski may not have been entirely clear in the copy previously filed and as the statements therein also may not have been entirely clear, a new Declaration of Dr. Lorberboum-Galski has now been prepared and is attached

hereto as Appendix C. As stated therein, it is the intent of the declarant that this Declaration supersede her previous Declaration. In this Declaration, Dr. Lorberboum-Galski states that the Met-GnRH of the present invention has a structure that is different from the GnRH used by Nett and that it has unexpectedly been discovered that this difference in structure allows a significant difference in selectivity and specificity of the two targeting molecules. She then explains that, when the plasmid shown at Figure 1C is expressed in a bacterial expression system, it will always result in a peptide in which the upstream GnRH sequence is preceded by Met residue. Thus, the amendment of the present specification to always refer to this targeting sequence as Met-GnRH, is not new matter. The targeting unit used in the conjugates of Nett is not bacterially produced and will not have a preceding Met.

The Declaration goes on to state that Nett discloses at column 12, lines 34-38, that the GnRH used for targeting in its invention targets the pituitary gland, and Nett states the gonadotropin-secreting cells of the anterior pituitary gland are the only cells to which the gonadotropin-releasing hormone of Nett's conjugates will bind. In contrast, the Met-GnRH of the present invention can selectively target cells having a distinctly different GnRH binding site which appears, for example, on adenocarcinomas. To clarify that the various cell lines disclosed in the experiments of the present specification are, indeed, adenocarcinomas, Dr. Lorberboum-

Galski refers to pages from the 1992 ATCC catalog that explicitly state that each of these cell lines are adenocarcinoma cell lines. Thus, the specification has been amended to make this explicit, and this is not new matter as such would have been inherent and a matter of common knowledge in the art.

Beginning at the last paragraph on page 5, the Declaration refers to experiments conducted to show the selectively of the Met-GnRH of the present invention and how it differs from that of the GnRH that is reported by Nett. Figures 1 and 2 of the Declaration use PCR using primers that will identify the standard GnRH receptor protein that appears on pituitary cells and is targeted by the conjugate of Nett. It can be seen from Figures 1 and 2 that this protein appears on human pituitary cells, as one would expect, and also appears on granulosa cell tumor cells. It does not appear on normal human lymphocytes or normal human granulosa cells, nor does it appear on Caco2 adenocarcinoma cells. Thus, the GnRH binding site appearing on adenocarcinoma cells is not the same receptor as is present on normal human pituitary cells.

The Declaration then explains that the chimeric protein of the present invention does not bind to and kill granulosa cell tumor cells despite the fact that they have the same GnRH receptor as appears on normal human pituitary cells (see Table 1 of the Declaration). However, the chimeric protein of the present invention does bind to and kill Caco2

adenocarcinoma cells, which do not have the same receptor as appearing on normal human pituitary cells.

These results are highly surprising and could not have been expected by any reading of Nett or Chaudhary. The experiments in the present specification further disclose that the chimeric protein of the present invention will bind to and kill colon adenocarcinoma cell lines, ovarian adenocarcinoma cell lines, breast adenocarcinoma cell lines, cervix adenocarcinoma cell lines and hepatocarcinoma cell lines (see Table 1 of the present specification). Additionally, it will kill various primary cultures specified in the specification (see Table 2 of the present specification). The Lorberboum-Galski Declaration attached hereto clarifies that each of these primary carcinomas have been identified as adenocarcinomas. It certainly would not be obvious from any reading of Nett or Chaudhary that any fusion protein obtained from the combination of those references would be able to kill adenocarcinomas directly, and particularly non-hormone related adenocarcinomas, such as colon adenocarcinomas.

The difference in the mechanism of action of the conjugates of Nett and the chimeric proteins of the present invention is explained at pages 9 and 10 of the attached Declaration. Nett does not state that the conjugate thereof will directly kill tumor cells. Nett discloses that the growth of hormone-dependent cancers, such as breast or prostate cancer, may be inhibited by administering the GnRH toxin conjugate of Nett by killing the pituitary cells and

thereby preventing the secretion of LH and FSH. As the cancers are sex-steroid dependent, the lack of secretion of the sex steroids will indirectly affect the growth of the cancer cells. This is quite different from the evidence of the present invention that the chimeric proteins directly bind to and kill adenocarcinoma cells, regardless of whether they are sex hormone-dependent. The attached Declaration also confirms that cell-killing moieties other than PE, which is specifically exemplified in the present specification, are also operable.

As the attached Declaration proves that the selectivity and specificity of the Met-GnRH chimeric proteins of the present invention are different from those of the GnRH conjugate of Mett, it is apparent that the difference in structure causes an unexpected difference in activity. As this would not have been predicted by any combination of Nett and the two Chaudhary references, any *prima facie* case of obviousness which may have been established by the examiner has been rebutted by a showing of unexpected results. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

In reviewing the present specification, myriad typographical and clerical errors were noted. Furthermore, it was believed that anyone of ordinary skill in the art reading the present specification would be able to understand the present invention better if the various carcinoma cell lines that are adenocarcinomas were specified as such, and if the

chimeric protein identified in the specification as GnRH-PE were amended to appear as Met-GnRH-PE. Accordingly, a substitute specification is being submitted herewith. Also attached hereto is a marked-up copy of the specification showing the changes that have been made therein. As all of the changes either correct obvious errors or make explicit that which had been implicit in the specification as filed, particularly as evidenced by the expert declaration of Dr. Lorberboum-Galski, none of the changes to the specification constitute prohibited new matter. The changes in paragraphs 21 and 23 merely clarify the statements that were originally made. As those of ordinary skill in the art reading the present specification as a whole would have understood that this was the intended meaning of the original wording, none of these changes constitute new matter.

In accordance with 37 C.F.R. §1.125(b)(1), the undersigned hereby states that the substitute specification includes no new matter. The examiner can verify this for himself by reviewing the marked-up version of the substitute specification submitted in accordance with 37 C.F.R. §1.125(b)(2) and 37 C.F.R. §1.121(b)(3)(iii). Entry and acceptance of this substitute specification are therefore respectfully urged.

Claims 30-34 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for reciting "starting with Met and having a glycine as the sixth amino

acid" because it is unclear how the protein can start with Met at position one and have a glycine at the sixth position.

The claims have now been amended to make it clear that Met is not part of the GnRH but that the chimeric protein of the present invention is preceded by a Met. Thus, Met is not one of the ten residues of GnRH and any recitation in the present claims to the glycine at the sixth position is no longer indefinite. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1-7, 9, 10 and 21-35 have been rejected as being unpatentable over Nett and further in view of Chaudhary 1989 and Chaudhary 1987 and Imai. The examiner states that Imai teaches the GnRH receptor on adenocarcinoma cells, endometrial carcinomas and other cancers and using GnRH analogs for therapy for malignancies. The examiner considers that it would have been *prima facie* obvious to have produced a fusion protein comprising the ten amino acids of GnRH ligated upstream to a mutated form of PE by recombinant methods and administering same to a patient for treatment of cancer. This rejection is respectfully traversed.

Imai adds nothing to the teachings of Nett and Chaudhary discussed hereinabove with respect to the unexpected selectivity and specificity of Met-GnRH as a targeting agent. The receptors identified by Imai are the same receptors that are on normal pituitary cells. The PCR used by Imai is directed to the same molecule as is the PCR that was used in the attached Lorberboum-Galski Declaration. There is no

suggestion therein that another GnRH binding site exists on adenocarcinoma and hepatocarcinoma cells and that the Met-GnRH of the present invention will target this different GnRH binding site. The fact that the chimeric protein of the present invention will bind to and kill adenocarcinoma cells that do not have the receptor studied by Imai but do not bind to granulosa cell tumors that do have the receptor studied by Imai (see the discussion of the Lorberboum-Galski Declaration, above) establishes the unexpected activity of the chimeric proteins of the present invention. Thus, as Imai adds nothing to the deficiencies of Nett and Chaudhary as discussed above, the unexpected results established herein rebut any *prima facie* case of obviousness which includes Imai for the same reason that the *prima facie* case of obviousness without Imai discussed above has been rebutted. Reconsideration and withdrawal of this rejection are therefore also respectfully urged.

Claims 33 and 34 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The examiner states that there is no support in the specification for a linking moiety being a linear protein or support to exclude all linking moieties. This rejection is respectfully traversed.

As the examiner points out, Figure 1 supports a chimeric protein that has no linker between the GnRH and the pE. Furthermore, the present specification states at paragraph 8 (of the substitute specification) that the

chimeric toxins of the present invention do not contain a chemical linking group. Thus, there is support in the present specification for claim 33 that specifies that the fusion protein has no linking moiety between the cell-killing moiety and the cell-targeting moiety. Claim 34 has now been canceled without prejudice, thus obviating this part of the rejection. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

It is submitted that all the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. §112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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